Circulating Tumor Cells (CTCs) in patients with extensive stage small cell lung cancer and their association with clinical outcome

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Abstract

Background: The NOTCH pathway has been identified as a key therapeutic pathway in SCLC. Tarextumab (TRXT, anti-Notch2/3, OMP-59R5) is a fully human monoclonal antibody that targets the Notch2 and Notch3 receptors. PINNACLE is a Phase 1b/2 trial of TRXT in combination with etoposide and platinum therapy (EP) in patients with untreated extensive stage small cell lung cancer (ES-SCLC). Baseline CTCs and post treatment changes in CTCs have previously been shown to predict the response to chemotherapy in SCLC. CTCs may also serve as pharmacodynamic (PD) biomarkers. Here we describe a study of baseline and longitudinal CTCs in ES-SCLC patients from the PINNACLE phase 1b trial (clinicaltrials.gov: NCT01859741).

Materials and methods: CTCs, CTC clusters, apoptotic CTCs and N-cadherin+ CTCs were identified and enumerated from patient blood samples using Epic Sciences CTC technology. Baseline CTCs from 26 patients were correlated with clinical outcome: progression-free survival (PFS), overall survival (OS) and best overall response (BOR), as well as metastatic status. A mixed effects model was used to investigate the post treatment changes in CTCs among the dose groups. Association of CTCs with PFS/OS and BOR, including CTCs at each time point, as well as temporal changes of CTC status, were studied. Multivariate analysis was performed to identify CTC numbers in a subset of time points to correlate with response to treatment.

Results: CTCs were present in 81% of the patients (21/26). CTC clusters and apoptotic CTCs were detected in 38% and 77% of the patients, respectively. At baseline, CTC counts ≥ 5/mL were significantly associated with poor OS (p=0.04). There was a trend that the presence of CTC clusters was associated with worse OS. With a cut-off of 3.4/mL, apoptotic CTCs showed a trend in association with overall survival. CTC numbers in patients with liver metastasis were significantly higher than in patients without liver metastasis. CTCs were also found to be correlated significantly with the number of metastatic sites. When measured at Day 7 post dosing, CTC numbers were significantly decreased.

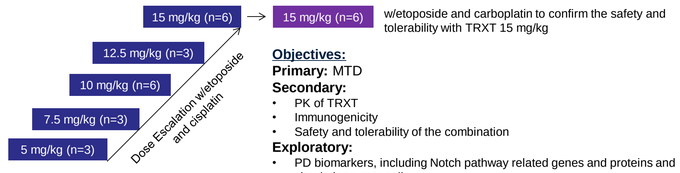
Conclusions: Our findings suggest that CTCs are frequently detectable in patients and are a prognostic factor in ES-SCLC. CTCs decrease with TRXT and platinum-based chemotherapy. Updated results will be presented. CTCs will be further evaluated in the Phase 2 portion of the PINNACLE trial.

Summary

- Baseline CTCs were associated with overall survival, liver metastasis and number of metastatic sites in PINNACLE Phase 1b patients.
- CTC numbers were significantly decreased at multiple time points taken at 7 days post dosing. Potential dose effects were observed.
- CTC numbers at cycle 1 day 8 post dosing appears to be the best predictor of PFS, OS and BOR.
- CTCs will be further evaluated in the PINNACLE Phase2 portion of the trial.

Phase 1b Study Schema and Objectives

TRXT, platinum IV Day 1, etoposide 100 mg/m^2 Days 1, 2, 3 of q21 days for 6 cycles, followed by TRXT alone in maintenance. DLT was assessed in the first 21 days. The initial dose escalation from TRXT 5 mg/kg to 15 mg/kg was done with etoposide and cisplatin (80 mg/m^2). Subsequently, a cohort of pts was treated with etoposide and carboplatin at AUC of 5 mg/mL.min with TRXT 15 mg/kg to confirm the safety and tolerability of carboplatin-based regimen with TRXT.



Objectives:

Primary: MTD

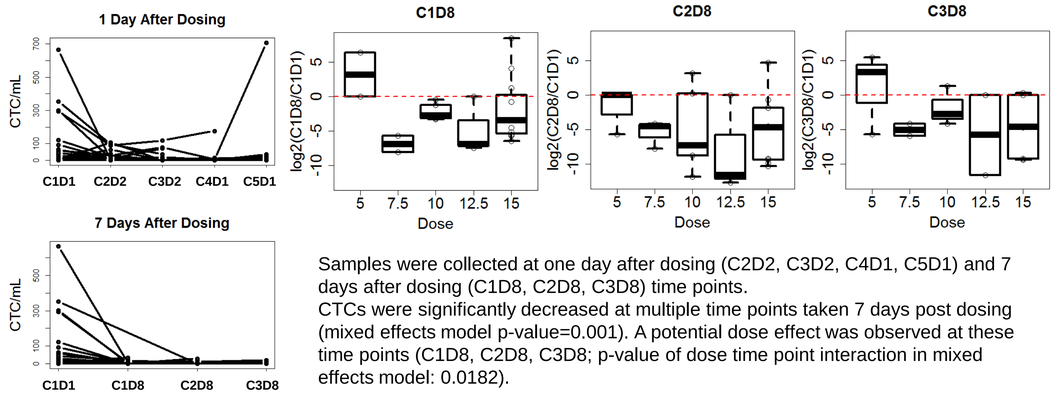
Secondary:

- PK of TRXT
- Immunogenicity
- Safety and tolerability of the combination

Exploratory:

- PD biomarkers, including Notch pathway related genes and proteins and circulating tumor cells

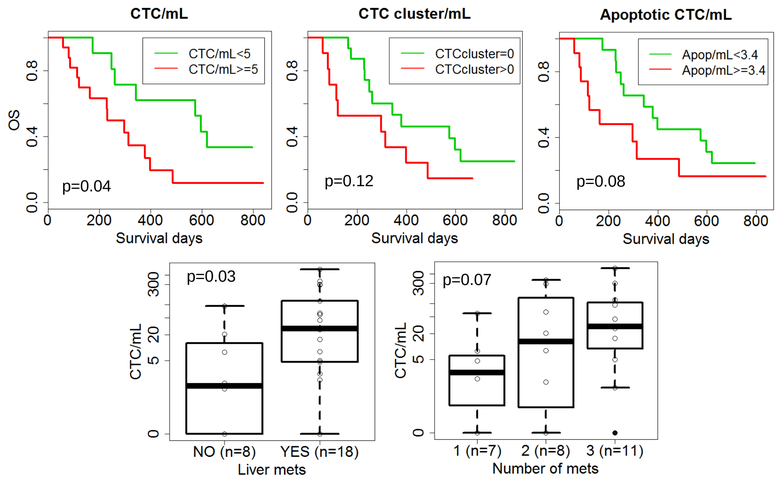
Potential PD Effect at 7 Days Post Dosing



Samples were collected at one day after dosing (C2D2, C3D2, C4D1, C5D1) and 7 days after dosing (C1D8, C2D8, C3D8) time points.

CTCs were significantly decreased at multiple time points taken 7 days post dosing (mixed effects model p-value=0.001). A potential dose effect was observed at these time points (C1D8, C2D8, C3D8; p-value of dose time point interaction in mixed effects model: 0.0182).

Baseline CTCs are Associated with Survival and Metastasis

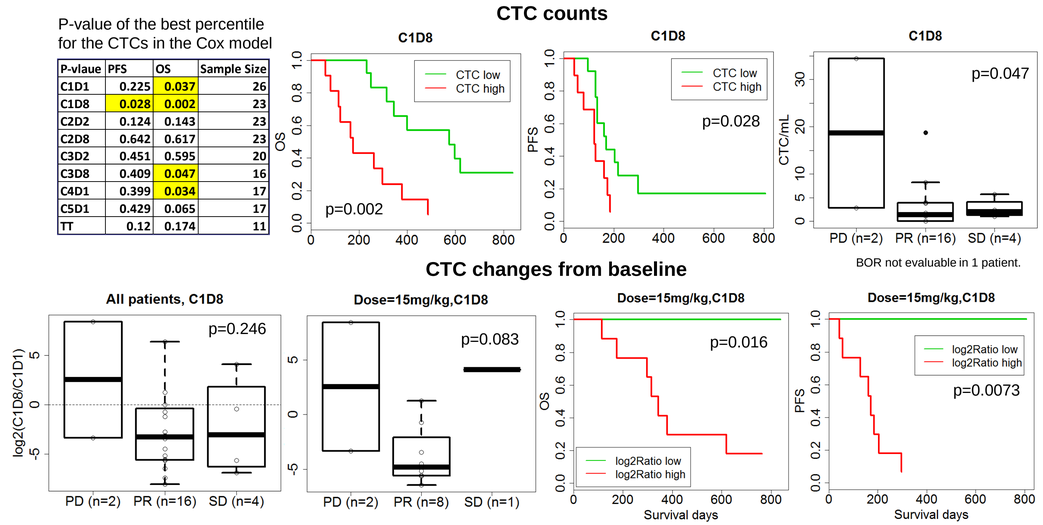


Baseline CTC counts were significantly associated with overall survival (CTC/mL<5: n=10; CTC/mL>=5: n=16). CTC clusters and apoptotic CTC counts showed a trend in association with overall survival (CTC cluster=0: n=16; CTC cluster>0: n=10; Apop/mL<3.4: n=15; Apop/mL>=3.4: n=11; Apop=apoptotic CTC). Baseline CTC counts were also associated with number of metastatic sites and liver metastasis.

Cycle 1 Day 8: Best Predictor of Outcome

P-value of the best percentile for the CTCs in the Cox model

P-vlaue	PFS	OS	Sample Size
C1D1	0.225	0.037	26
C1D8	0.028	0.002	23
C2D2	0.124	0.143	23
C2D8	0.642	0.617	23
C3D2	0.451	0.595	20
C3D8	0.409	0.047	16
C4D1	0.399	0.034	17
C5D1	0.429	0.065	17
TT	0.12	0.174	11



CTC counts (top): CTC counts at cycle 1 day 8 (C1D8) post dosing are significantly associated with clinical outcome.

CTC changes from baseline (bottom): In the 15mg/kg group, the log2 ratio at C1D8 was significantly associated with PFS and OS, and marginally associated with BOR, while the association with outcome was not significant in all 26 patients.

Cut-offs for separating biomarker high vs. low in all the survival curves were based on the most significant percentiles associated with survival. Top: 55% (low: n=13; high: n=10); Bottom: 30% (low: n=3; high: n=8).